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Article

ARTICLE

# Familial Risks and Mortality in Second Primary Cancers in Melanoma

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## Abstract

**Background:** Malignant melanoma (MM) patients are at increasing risk of developing second primary cancers (SPCs). We assessed mortality and risk of SPCs in MM patients with siblings or parents affected with same cancer compared with that of the general population.
**Methods:** We used the Swedish Family-Cancer Database to assess relative risks (RRs) and causes of death in SPCs until 2015 in patients with a MM diagnosis between 1958 and 2015. We identified 35 451patients with MM among whom 3212 received a subsequent diagnosis of SPC. RRs of SPCs after MM diagnosis were calculated stratifying over concordant family history of cancer in first-degree relatives.
**Results:** Familial RRs were increased for second melanoma (RR = 19.28, 95% CI = 16.71 to 22.25), squamous cell skin cancer (RR = 7.58, 95% CI = 5.57 to 10.29), leukemia (RR = 5.69, 95% CI = 2.96 to 10.94), bladder (RR = 4.15, 95% CI = 2.50 to 6.89), ovarian (RR = 3.89, 95% CI = 1.46 to 10.37), kidney cancer (RR = 3.77, 95% CI = 1.57 to 9.06), cancer of unknown primary (RR = 3.67, 95% CI = 1.65 to 8.16), nervous system (RR = 2.88, 95% CI = 1.20 to 6.93), breast (RR = 2.34, 95% CI = 1.92 to 2.84), lung (RR = 2.24, 95% CI = 1.50 to 3.35), and prostate cancer (RR = 2.22, 95% CI = 1.89 to 2.61) with statistical significance. For all cancers, familial RR was in excess (2.09, 95% CI = 2.02 to 2.16 vs 1.78, 95% CI = 1.69 to 1.87; $P_{trend} < .0001$). Cause of death in MM patients with SPC is shown to be dependent on the cancer site though SPCs contributed to majority of deaths.
**Conclusions:** SPCs appear higher with prior family history of cancer and contribute to mortality. SPC was the most common cause of death in patients with SPC and is almost uniformly the major contributing cause of death for all cancer sites. For improved survival in MM patients, prevention and early detection of SPCs would be important.

Survival rates among patients with malignant cutaneous melanoma (MM) have improved with a resulting increased likelihood for occurrence of second primary cancers (SPCs). SPCs in patients with MM account for 5.1% of all SPCs in Sweden and 3.9% in Germany (1). Patients with MM are at an increased risk of multiple MMs and at least 10 different types of other (discordant) SPCs (2,3). Multiple MMs signal increased familial susceptibility to MM, and multiple cancers, even the discordant ones, are often associated with genetic predisposition (2,4). Thus, known cancer syndromes manifesting MM also show an excess of some other cancers (5). The most common high-risk gene predisposing to MM is *CDKN2A*, which is also associated with pancreatic cancer (5). Germline mutations in breast cancer 1 associated protein 1 also cause predisposition to MM, but the mutations are relatively more important in rare cancers (uveal melanoma and mesothelioma) constituting a novel cancer syndrome (5–7). In addition to the high-risk genes, genome-wide association studies have identified more than 20 loci that predispose to MM (8). These are involved in pathways related to nevus count, pigmentation, telomere homeostasis, tumor suppression, and DNA repair; some of these are also associated with other cancers (9). Family studies have shown that MM is

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associated at the population level with breast, prostate, colorectal, skin squamous cell (SCC), and nervous system cancers (10,11). Direct evidence on the effect of family history on SPCs was recently demonstrated in Hodgkin lymphoma where an excess of second lung, colorectal, and breast cancers was found in survivors with a family history of these cancers (12). In cancers with good survival, SPCs are an important cause of death (13,14).

In the present study, we focus on risk for and mortality in SPCs and higher order multiple primary cancers in patients with MM, hypothesizing that family history of cancer X in patients with MM increases the risk for cancer X as an SPC. A first-degree family history of any cancer is common in MM patients because 6.3% of patients have a family member diagnosed with MM and 52% of them have a family history of some other form of cancer (15). We used data from the most recent version of the Family-Cancer Database, which covers the Swedish population for more than a century and linked cancers for 58 years from the national cancer registry. The effect of multiple primaries, particularly of SPCs, was remarkably high on disease outcome. Any attempt to increase survival in MM needs to counter the challenge of SPCs.

## Methods

Data for our study were obtained from the Swedish Family-Cancer Database, which includes information about the residents of Sweden organized in family datasets and covers more than a century (16). Individuals were linked to the national cancer registry for first and any subsequent cancers (16). The database records cancers according to the International Classification of Diseases 7th revision (ICD-7) and later revisions. Until the end of 2015, more than 2 million cancers were recorded among 16.1 million individuals; 8.8 million individuals belonged to the 0- to 83-year-old offspring generation (born after 1931) for which relative risks (RRs) were calculated.

### Statistical Analysis

We followed newly diagnosed patients with MM from January 1, 1958 until December 31, 2015 for diagnosis of any of the 35 different SPCs, including second MMs. Family history was called when the SPC was the same, concordant cancer diagnosed in a first-degree relative (parent or sibling). Family history was recorded from the beginning of cancer registration in Sweden from the year 1958 onwards. The follow-up was terminated at diagnosis of SPC, emigration, death, or December 31, 2015 (when the oldest individuals reached age 83 years), whichever occurred first. Causes of death were also available in the database as obtained from the national causes of death register. Familial and nonfamilial RRs of SPC were estimated comparing risk (incident rate) of SPC among MM survivors, with or without prior family history, against risk of that cancer in the general population. Waiting time distribution with Poisson assumption was employed to estimate RRs and corresponding confidence intervals (CIs) for 5%, 1%, and 0.1% levels of statistical significance. A generalized linear multivariable model was used with regressors including age group, sex, calendar period, residential area, and socioeconomic status as adjustments for potential confounding.

The underlying cause of death is ascertained by amalgamation of the cancer registry and the death certificate notification (17). This is annotated with the following ICD codes from 1997 onwards: ICD-7 (1958–1968), ICD-8 (1969–1986), ICD-9 (1987–1996), and ICD-10. All cancer-related deaths were stratified into MM, SPC, "other cancer," and non-neoplastic cause of death "other causes." For patients with multiple MMs, it was not possible to define which MM caused the patient's death. "Other cancer" includes cases diagnosed at the issue of death certificates, referred to as "death certificate notifications" (17–19). These notifications are not used by the Swedish Cancer Registry to complement cancer data in contrast to that of the other Nordic Cancer Registries (17–19). We have found that the notifications often included multiple cancers and cancer of unknown primary (CUP). In our previous studies, we have used these as information on metastases (20,21). If the death certificate notification matched the organ site of the reported primary cancer, it was classified to that site. In some cases when such an assignment could not be made, the classification was considered "other cancer."

Survival probabilities and hazard ratios were estimated subject to conformity to proportional hazard assumption with Cox regression, adjusted for sex, residential area, and socioeconomic status stratified over diagnosis of SPC and family history of cancer. Although the nationwide database does not include data on possible individual risk factors of cancer, adjustment for socioeconomic status helps to control for a number of social class-related risk factors, including smoking (22,23). Population attributable fraction (PAF) was employed to estimate the effect of family history of cancer on total disease burden. It was assessed with RRs where PAF = proportion of population with family history $\times$ [1 – $RR_{(fh-)}$ / $RR_{(fh+)}$]; $RR_{fh(+/-)}$ indicates RR with/without cancer family history. All statistical analyses were done with R version 3.4 and SAS version 9.4.

The study was approved by the Ethical Committee of Lund University without requirement for informed consent. Through advertisements in the major newspapers, people could choose to opt out before the research database was constructed. The project database is located at Center for Primary Health Care in Malmö, Sweden.

## Results

A total of 8.8 million individuals belonging to the offspring generation with full parental history contributed to the study cohort; 35 451 (47% male) developed MM at 51 years of median age at diagnosis (Table 1). Among MM survivors, with 6 years of median follow-up, 4724 (13.3%) developed SPCs including 3212 (67.9%) with a family history of cancer. Of patients with SPC, 823 (17.4%) later went on to develop a third primary cancer, 172 (3.6%) of them developed a fourth primary cancer, and 60 (1.3%) developed a fifth primary cancer. The total number of deaths by the end of 2015 among all MM patients was 5259 (14.8%); of these, 3877 (73.7%) occurred in patients without SPC and 1382 (29.3%) of those with SPCs. In patients without SPC, 74.2% of the deaths were due to MM, but in patients with SPC only 24.5% of deaths were due to MM while the majority of deaths (53.1%) were due to second and higher order multiple primaries.

In Table 2 we compared RRs of SPCs in patients with MM depending on a family history of concordant cancer (or of any cancer in the last line). SPCs were listed when two or more familial cases were found. The RRs were statistically significant for family history for 11 SPCs, including lung, breast, ovarian, prostate, kidney, bladder, skin (SCC) and nervous system cancers, melanoma, leukemia, and CUP. The highest risk for familial SPC was for melanoma (RR familial

**Table 1.** Demographic summary of study population

| Total No. of individuals followed | 8.8 million | |
|---|---|---|
| Summary of cases | | |
| Number of melanoma diagnoses | 35 451 | |
| Males | 16 659 (47.0%) | |
| Females | 18 792 (53.0%) | |
| Median age at first cancer diagnosis, y | 51 [40–62]* | |
| SPC diagnoses among melanoma survivors | 4724 | |
| Median follow-up time until SPC diagnosis, y | 6 [2–15] | |
| Number of familial cases of SPC (family history of any cancer) | 3212 | |
| Median total follow-up time since melanoma diagnosis, y | 8 [3–16] | |
| 3rd and higher order primaries | | |
| 3rd primary cancer diagnosis | 823 | |
| 4th primary cancer diagnosis | 172 | |
| 5th primary cancer diagnosis | 60 | |
| Summary of deaths till end of 2015 | | |
| Total no. of deaths among melanoma patients | 5259 (14.8% of all patient) | |
| Total deaths among patients without SPC | 3877 (12.6% of all patient) | |
| Total deaths among patients with SPC | 1382 (29.3% of all patient) | |
| Summary of causes of death | Patients with SPC | Patients without SPC |
| Deaths due to first primary cancer | 339 (24.5%) | 2875 (74.2%) |
| Deaths due to SPC | 596 (43.1%) | — |
| Deaths due to higher order multiple primary cancer | 138 (10.0%) | — |
| Deaths due to other cancer | 100 (7.2%) | 156 (4.0%) |
| Deaths due to other cause | 209 (15.1%) | 846 (21.8%) |
| Total deaths | 1382 | 3877 |

*Square bracket indicates inter-quartile range in years. SPC = second primary cancer.

**Table 2.** Familial risk of second primary cancers among MM survivors

| | Number of first degree relatives with cancer at a concordant site | | | | |
|---|---|---|---|---|---|
| | ≥1 | | 0 | | |
| Second cancer | No. | RR (95% CI) | No. | RR (95% CI) | $P_{trend}$ |
| Colorectum | 31 | 1.28 (0.90 to 1.83) | 246 | 1.16* (1.02 to 1.31) | .29 |
| Liver | 2 | 2.08 (0.52 to 8.32) | 39 | 0.94 (0.69 to 1.29) | .23 |
| Pancreas | 3 | 2.54 (0.82 to 7.88) | 44 | 0.85 (0.63 to 1.15) | .19 |
| Lung | 24 | 2.24‡ (1.50 to 3.35) | 179 | 1.07 (0.92 to 1.24) | .01 |
| Breast | 99 | 2.34 (1.92 to 2.84) | 458 | 1.34‡ (1.22 to 1.47) | <.001 |
| Endometrium | 4 | 2.40 (0.90 to 6.40) | 75 | 1.06 (0.85 to 1.33) | .16 |
| Ovary | 4 | 3.89† (1.46 to 10.37) | 48 | 1.07 (0.80 to 1.41) | .04 |
| Prostate | 150 | 2.22‡ (1.89 to 2.61) | 522 | 1.13† (1.04 to 1.23) | <.001 |
| Kidney | 5 | 3.77† (1.57 to 9.06) | 74 | 1.50‡ (1.19 to 1.88) | .04 |
| Bladder | 15 | 4.15 (2.50 to 6.89) | 110 | 1.28* (1.06 to 1.54) | .01 |
| Melanoma | 189 | 19.28 (16.71 to 22.25) | 1182 | 9.21‡ (8.72 to 9.73) | <.001 |
| Skin SCC | 41 | 7.58 (5.57 to 10.29) | 321 | 3.50‡ (3.13 to 3.91) | <.001 |
| Nervous system | 5 | 2.88* (1.20 to 6.93) | 120 | 1.79‡ (1.49 to 2.14) | .03 |
| Endocrine glands | 2 | 3.51 (0.88 to 14.04) | 66 | 1.77‡ (1.39 to 2.25) | .33 |
| Non-Hodgkin Lymphoma | 4 | 2.11 (0.79 to 5.61) | 136 | 1.93‡ (1.63 to 2.29) | .19 |
| Leukemia | 9 | 5.69‡ (2.96 to 10.94) | 87 | 1.46‡ (1.18 to 1.80) | .03 |
| CUP | 6 | 3.67† (1.65 to 8.16) | 122 | 2.21‡ (1.85 to 2.65) | .03 |
| All non-melanoma cancers | 2223 | 1.83‡ (1.75 to 1.91) | 1130 | 1.46‡ (1.37 to 1.56) | <.001 |
| All | 3212 | 2.09‡ (2.02 to 2.16) | 1512 | 1.78‡ (1.69 to 1.87) | <.001 |

*P = .05 CI = 95% confidence interval; CUP = cancer of unknown primary; MM = malignant cutaneous melanoma; RR = relative risk; SCC = squamous cell carcinoma; SPC = second primary cancer
†P = .01.
‡P = .001.

=19.28 vs RR nonfamilial = 9.21), followed by skin SCC (RR familial = 7.58 vs RR nonfamilial = 3.50), leukemia (RR familial = 5.69 vs RR nonfamilial = 1.46) and cancers of the bladder (RR familial = 4.15 vs RR nonfamilial = 1.28), ovary (RR familial = 3.89 vs RR nonfamilial = 1.07), and kidney (RR familial = 3.77 vs RR nonfamilial = 1.50) and CUP (RR familial = 3.67 vs

RR nonfamilial = 2.21). For other SPCs with statistically significant excess risks, the familial RRs were consistently more than 2.0. The largest contributions of familial SPCs were observed for melanoma (n = 189), prostate (n = 150), and breast (n = 99) cancers. The RR for any familial SPC (n = 3212, 68.0% of all MM patients) was 2.09 (95% CI = 2.02 to 2.16) compared with 1.78 (95% CI = 1.69 to 1.87) without family history (n = 1512, $P < .001$). We can estimate that the PAF for family history was 10.1%, which would account for 477 extra patients with SPC.

Familial risks for most cancers were higher when MM was diagnosed in relatively young patients, but because of small numbers none of the differences were statistically significant (ie, 95% CIs overlapped; Supplementary Table 1, available online). When the cutoff age for MM diagnosis was 50 years, patients with a family history of MM showed a risk of 20.11 (95% CI = 16.49 to 24.52) for the early diagnostic group compared with 18.43 (95% CI = 14.99 to 22.65) in the late group. The difference in RRs was relatively large for a family history of lung cancer (2.99, 95% CI = 1.69 to 5.27 vs 1.79, 95% CI = 1.01 to 3.16). When the cutoff was at 60 years, the difference in RRs for lung cancer was even larger (2.62, 95% CI = 1.67 to 4.11 vs 1.45, 95% CI = 0.60 to 3.48). For family histories of endometrial, ovarian, and kidney cancers, all MM cases were in the early onset group and the RRs ranged from 3.58 to 5.72.

Of 1382 deaths in patients with SPC, 596 (43.1%) were due to SPC and 138 (10.0%) were due to higher order multiple primaries (Table 3). Only the sites with at least five total deaths are listed although the total includes all the 35 sites. The cause of death in MM patients with SPC was highly dependent on the site of SPC. The highest contributions to causes of death were observed for lung (87.0%) and pancreatic (86.0%) cancers, multiple myeloma (85.0%), and ovarian (81.0%) and esophageal (80.0%) cancers. Apart from skin (SCC), endocrine gland, and connective tissue cancers, SPCs at all the other sites contributed a higher proportion of deaths compared with MM. For death due to "other cancer," CUP showed the highest proportion, 32.7%, followed by endometrial (25%), connective tissue, and cervical cancers (both 22.2%). These results are summarized for the eight most common SPCs and all SPCs in Figure 1.

Survival data are shown in Figure 2 for patients with and without SPC and any family history. There was no difference in the initial survival rates for patients, with and without SPCs, because SPCs were diagnosed in the course of time (median to SPC 6 y). However, after approximately 10 years of follow-up, survival curves diverged with marked poorer survival for patients with SPC compared with those without while family history showed a minor negative effect. Compared with a baseline hazard of 1.00 for patients without SPC or family history (n = 1374), the hazard ratio for patients without SPC but with family history was 1.13 (n = 2503; 95% CI = 1.09 to 1.16) and that for patients with SPC were 1.97 without family history (n = 462; 95% CI = 1.89 to 2.04) and 2.04 with family history (n = 920; 95% CI = 1.99 to 2.10).

## Discussion

Using data from the Swedish Family-Cancer Database, the present study covered all diagnoses of SPCs in patients with MM with a maximum possible follow-up of 58 years starting from 1958. The results offered several novel observations of clinical importance. Firstly, more than two-thirds (68%) of all MM patients with SPC had a first-degree family history of any cancer; this increased the risk from 1.78 to 2.09. The familial risk was moderately higher in MM patients diagnosed at a relatively early age. Secondly, for 11 SPCs, risk of concordant family history was statistically significantly increased, being remarkably high for melanoma (19.28 vs 9.21), which also resulted in the largest number of familial cases. However, high and statistically significant familial risks were observed for other cancers, including prostate, breast, and skin (SCC) cancers. Thirdly, irrespective of family history, patients with SPCs experienced increased mortality. Fourthly, mortality was highest for SPCs, which are known to be fatal as primary cancers. A limitation of the study was that the oldest individual in the present cohort reached age 83 years at the end of 2015, and it is likely that additional SPCs were/will be diagnosed past the follow-up time whereby the present results may not have been able to catch the full scope of SPCs in this cohort of patients (1).

SPCs in patients with MM have been reported in many previous studies as discussed in the introduction. In the present cohort, 13.3% of the patients were diagnosed with SPC. Therapy-related causes of SPCs are likely to be small for MM because surgery is the main mode of treatment for localized disease. Environmental causes, such as chronic exposure to ultraviolet radiation, may be an important cause for SPC in skin (SCC). Family members also share other environmental/behavioral risk factors, but not many of these are known to predispose to MM. Genetic causes could also be plausible, but among high-risk genes only mutations in cyclin-dependent kinase inhibitor 2 A *CDKN2A* are prevalent in MM families (24). Mutations in other genes, such as cyclin-dependent kinase 4, breast cancer 1 associated protein 1, telomere maintenance genes (*TERT*, *POT1*, *TERF2IP*, and *ACD*), DNA damage repair genes (*PARP1*, *ATM*), and other nevi and pigmentation-specific genes are rare in MM and predispose to a limited number of other cancers, yet these mutations may confer a high risk in the affected individuals (25–27). Thus with the exception of SPCs in MM and skin (SCC), no known genes or environmental factors can be invoked to explain the extensive familial association for SPCs. However, data from this database have shown that there is a general increase in familial risk in families with multiple diverse cancers (15). A consistent increased risk of melanoma was reported in families where breast, prostate, colorectal, skin, and nervous system cancers were diagnosed (10).

Survival was drastically worse for patients with SPC, and hazard ratios increased from 1.0 in patients without SPCs to 2.0 for patients with SPCs. Family history was a minor predictor of survival, but family history contributed to increased numbers of SPCs, accounting for a PAF of 10.1%.

Mortality patterns in MM patients were distinct depending on diagnosis of SPC. Among MM patients without SPC, 74.2% died of MM and 21.8% of other causes. On the contrary, 53.1% of patients with a subsequent primary cancer diagnosis died because of SPC or higher order primaries and 24.5% of deaths were due to MM. Deaths due to other cancers accounted for 7.2% of all casualties; these were ascertained from death certificate notifications and amounted to only 4.0% in patients without SPC. It can be suspected that at least some of these other cancers may be metastases originating from earlier cancer diagnoses. We observed high RRs for CUP in MM patients with or without a family history. CUP is characterized as fatal metastatic cancer originating in an unknown site. We have previously shown familial clustering of several primary tumors, including MM, with CUP, speculating that the associated familial cancer may disclose the origin of CUP cells (28,29). Figure 1

**Table 3.** Distribution of cause of deaths in patients with MM diagnosed with multiple primary cancers*

| | 2nd primary cancer | 1st primary cancer (MM) | Higher order multiple primary cancers | Other cancer | Other causes |
|---|---|---|---|---|---|
| Cancer | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) |
| UAT | 7 (36.8) | 4 (21.1) | 2 (10.5) | 2 (10.5) | 4 (21.1) |
| Esophagus | 12 (80.0) | | | 2 (13.3) | 1 (6.7) |
| Stomach | 9 (64.3) | 3 (21.4) | | 2 (14.3) | |
| Small intestine | 4 (40.0) | 1 (10.0) | 1 (10.0) | 1 (10.0) | 3 (30.0) |
| Colorectum | 90 (74.4) | 9 (7.4) | 6 (5.0) | 3 (2.5) | 13 (10.7) |
| Liver | 19 (70.4) | | | 3 (11.1) | 5 (18.5) |
| Pancreas | 37 (86.0) | 1 (2.3) | 1 (2.3) | 2 (4.7) | 2 (4.7) |
| Lung | 134 (87.0) | 4 (2.6) | 6 (3.9) | 3 (1.9) | 7 (4.5) |
| Breast | 54 (44.6) | 22 (18.2) | 19 (15.7) | 3 (2.5) | 23 (19.0) |
| Cervix | 5 (55.6) | 2 (22.2) | | 2 (22.2) | |
| Endometrium | 3 (25.0) | 1 (8.3) | | 3 (25.0) | 5 (41.7) |
| Ovary | 17 (81.0) | 1 (4.8) | 1 (4.8) | 2 (9.5) | |
| Other female genitals | 3 (50.0) | 2 (33.3) | | 1 (16.7) | |
| Prostate | 32 (28.8) | 28 (25.2) | 16 (14.4) | 5 (4.5) | 30 (27.0) |
| Kidney | 17 (58.6) | 8 (27.6) | 2 (6.9) | 1 (3.4) | 1 (3.4) |
| Bladder | 24 (61.5) | 5 (12.8) | 4 (10.3) | 1 (2.6) | 5 (12.8) |
| Melanoma | | 140 (59.1) | 47 (19.8) | 7 (3.0) | 43 (18.1) |
| Skin (SCC) | 2 (2.9) | 28 (40.6) | 10 (14.5) | 3 (4.3) | 26 (37.7) |
| Nervous system | 42 (60.9) | 6 (8.7) | 6 (8.7) | 9 (13.0) | 6 (8.7) |
| Thyroid gland | 4 (33.3) | 1 (8.3) | 3 (25.0) | | 4 (33.3) |
| Endocrine glands | 2 (15.4) | 2 (15.4) | 3 (23.1) | 2 (15.4) | 4 (30.8) |
| Connective tissue | 1 (11.1) | 3 (33.3) | | 2 (22.2) | 3 (33.3) |
| NHL | 28 (54.9) | 9 (17.6) | 4 (7.8) | 1 (2.0) | 9 (17.6) |
| Multiple myeloma | 17 (85.0) | 2 (10.0) | 1 (5.0) | | |
| Leukemia | 12 (35.3) | 9 (26.5) | 1 (2.9) | 3 (8.8) | 9 (26.5) |
| CUP | 19 (18.8) | 43 (42.6) | 2 (2.0) | 33 (32.7) | 4 (4.0) |
| Total | 596 (43.1) | 339 (24.5) | 138 (10.0) | 100 (7.2) | 209 (15.1) |

*CUP = cancer of unknown primary; MM = malignant cutaneous melanoma; NHL = non-Hodgkin lymphoma; SCC = squamous cell carcinoma; UAT = upper aerodigestive tract.

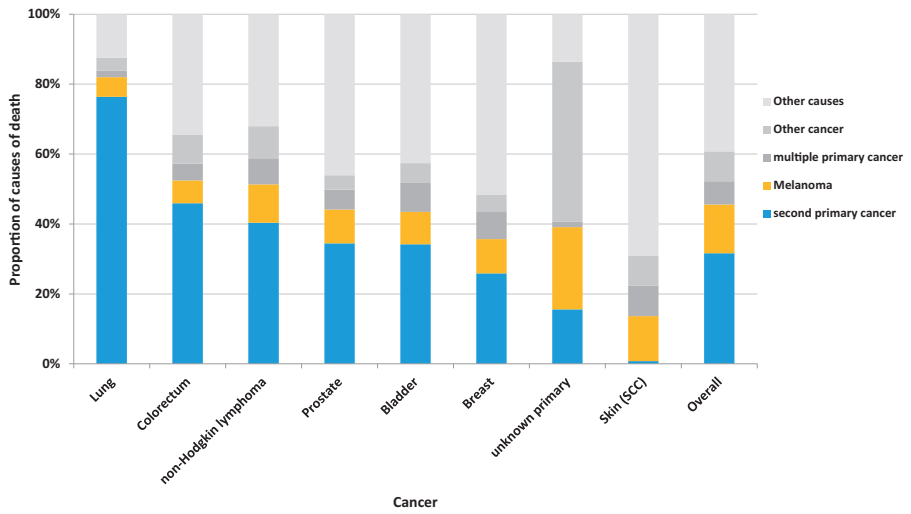


**Figure 1.** Distribution of causes of death for eight common and all second primary cancers together among malignant cutaneous melanoma survivors. CUP = cancer of unknown primary; SCC = squamous cell carcinoma. Data are presented in Table 3.

showed that CUP had the largest proportion of deaths due to other cancer (32.7%).

What are the clinical take-home messages from this study? SPCs will increase in accordance with increasing survival in MM, and the present proportion of 13.3% of patients coming down with a SPC is an underestimate due to incomplete follow-up time, particularly towards the termination of the study with the highest incidence of MM. SPCs are often fatal whereas prevention and early detection may be life-saving. The most common SPC was MM, and follow-up of MM patients should be a necessity, and those with a family history should be flagged. Skin (SCC) cancer is easily surveyed together with

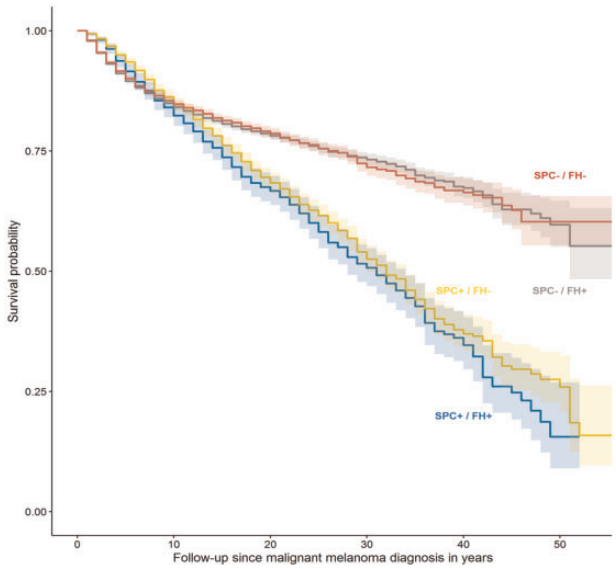


**Figure 2.** Survival probabilities stratified over second primary cancer diagnosis and family history of cancer are plotted against time of follow-up in years since diagnosis of malignant cutaneous melanoma. FH (+/-) = with or without family history of cancer; SPC (+/-) = presence or absence of second primary cancer diagnosis.

MM. For other common SPCs, prostate and breast cancers, taking a family history will help to devise and agree on a management plan with the patients. A family history of lung cancer may signal a risk of SPC and advice about smoking could be appropriate.

In conclusion, we showed that second and higher order multiple primaries caused more than half of the deaths in MM patients with an SPC. Family history of lung, ovary, kidney, bladder, and skin (SCC) cancer and leukemia more than doubled the risk of SPC. In agreement with previous reports, a family history of MM led to an almost 20-fold increased risk of second MM. Mortality was largely governed by the type of SPC. For improved survival in MM, prevention of SPCs should be a primary target, which should start with a thorough family history following diagnosis of MM.

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## Notes

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